HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use INTUNIV™ safely and effectively. See full prescribing information for INTUNIV™ .

INTUNIV™ (guanfacine) extended-release tablets
Initial U.S. Approval: 1986

INDICATIONS AND USAGE

INTUNIV™ is a selective alpha$_{2A}$-adrenergic receptor agonist indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

The efficacy of INTUNIV™ is based on results of two 8 to 9 week studies in children and adolescents (14.1). Maintenance treatment has not been systematically evaluated, and patients who are continued on longer-term treatment require periodic reassessment (1).

DOSAGE AND ADMINISTRATION

For all patients (2.1):
- Dose once daily.
- Tablets should not be crushed, chewed or broken before swallowing.
- Do not administer with high-fat meals, because of increased exposure.
- Do not substitute for immediate-release guanfacine tablets on a mg-per-mg basis, because of differing pharmacokinetic profiles.

Dose selection (2.2):
- If switching from immediate-release guanfacine, discontinue that treatment and titrate with INTUNIV™ as directed.
- Begin at a dose of 1 mg once daily and adjust in increments of no more than 1 mg/week.
- Maintain the dose within the range of 1-4 mg/day, depending on clinical response and tolerability.
- Consider dosing on a mg/kg basis. Improvements observed at starting doses of 0.05-0.08 mg/kg once daily. Doses up to 0.12 mg/kg once daily may provide additional benefit.
- Doses above 4 mg/day have not been studied.

Discontinuation (2.4):
- When discontinuing taper the dose in decrements of no more than 1mg every 3 to 7 days.

DOSAGE FORMS AND STRENGTHS

- Extended-release tablets: 1 mg, 2 mg, 3 mg and 4 mg (3)

CONTRAINDICATIONS

- History of hypersensitivity to INTUNIV™, its inactive ingredients, or other products containing guanfacine (e.g. TENEX®)(4).

WARNINGS AND PRECAUTIONS

- Hypotension, bradycardia, and syncope: Use INTUNIV™ with caution in patients at risk for hypotension, bradycardia, heart block, or syncope (e.g., those taking antihypertensives). Measure heart rate and blood pressure prior to initiation of therapy, following dose increases, and periodically while on therapy. Advise patients to avoid becoming dehydrated or overheated (5.1).
- Sedation and somnolence: Occur commonly with INTUNIV™. Consider the potential for additive sedative effects with CNS depressant drugs. Caution patients against operating heavy equipment or driving until they know how they respond to INTUNIV™ (5.2).
- Other guanfacine-containing products: Do not use INTUNIV™ concomitantly with other products containing guanfacine (e.g., Tenex) (5.3).

ADVERSE REACTIONS

Most common and dose-related adverse reactions: somnolence, sedation, abdominal pain, dizziness, hypotension/decreased blood pressure, dry mouth and constipation (6).

To report SUSPECTED ADVERSE REACTIONS, contact Shire US Inc. at 1-800-828-2088 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

To report SUSPECTED ADVERSE REACTIONS, contact at or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- CYP3A4/5 inhibitors (e.g., ketoconazole): Coadministration may increase rate and extent of guanfacine exposure. Use concomitantly with caution. (7.1).
- CYP3A4 inducers (e.g., rifampin): Coadministration may decrease rate and extent of guanfacine exposure. Consider dose increase of INTUNIV™ (7.2).
- Valproic acid: Coadministration may increase serum valproic acid concentrations (7.3).
- Antihypertensive drugs: Use caution when coadministered with INTUNIV™ (5.1, 7.4).
- CNS depressants: Use caution when coadministered with INTUNIV™ (5.2, 7.5).

USE IN SPECIFIC POPULATIONS

- Hepatic or Renal Impairment: dose reduction may be required in patients with clinically significant impairment of hepatic or renal function (8.6).

See 17 for PATIENT COUNSELING INFORMATION

Revised: 08/2009

FULL PRESCRIBING INFORMATION: CONTENTS *

*** Sections or subsections omitted from the full prescribing information are not listed**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

INTUNIV™ is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). The efficacy of INTUNIV™ was studied for the treatment of ADHD in two controlled clinical trials (8 and 9 weeks in duration) in children and adolescents ages 6-17 who met DSM-IV® criteria for ADHD [see *Clinical Studies (14)*]. The effectiveness of INTUNIV™ for long-term use (more than 9 weeks) has not been systematically evaluated in controlled trials.

A diagnosis of ADHD implies the presence of hyperactive-impulsive and/or inattentive symptoms that cause impairment and were present before the age of 7 years. The symptoms must cause clinically significant impairment, e.g., in social, academic, or occupational functioning, and be present in two or more settings, e.g., school (or work) and at home. The symptoms must not be better accounted for by another mental disorder. For the Inattentive Type, at least six of the following symptoms must have persisted for at least 6 months: lack of attention to details/careless mistakes; lack of sustained attention; poor listener; failure to follow through on tasks; poor organization; avoids tasks requiring sustained mental effort; loses things; easily distracted; forgetful. For the Hyperactive-Impulsive Type, at least six of the following symptoms must have persisted for at least 6 months: fidgeting/squirming; leaving seat; inappropriate running/climbing; difficulty with quiet activities; "on the go"; excessive talking; blurting answers; can't wait turn; intrusive. The Combined Type requires both inattentive and hyperactive-impulsive criteria to be met.

Special Diagnostic Considerations

Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but also of special psychological, educational, and social resources. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the patient and not solely on the presence of the required number of DSM-IV® characteristics.

Need for Comprehensive Treatment Program

INTUNIV™ is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, and social) for patients with this syndrome. Drug treatment may not be indicated for all patients with this syndrome. INTUNIV™ is not intended for use in patients who exhibit symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis. Appropriate educational/vocational placement is essential and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe INTUNIV™ will depend upon the physician's assessment of the chronicity and severity of the patient's symptoms and on the level of functional impairment.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

INTUNIV™ is an extended-release tablet and should be dosed once daily. **Tablets should not be crushed, chewed or broken before swallowing because this will increase the rate of guanfacine release.** Do not administer with high fat meals, due to increased exposure.

Do not substitute for immediate-release guanfacine tablets on a mg-mg basis, because of differing pharmacokinetic profiles. INTUNIV™ has a delayed T_{max}, reduced C_{max} and lower bioavailability compared to those of the same dose of immediate-release guanfacine [see *Clinical Pharmacology (12.3)*].

2.2 Dose Selection

If switching from immediate-release guanfacine, discontinue that treatment, and titrate with INTUNIV™ according to the following recommended schedule.

Begin at a dose of 1 mg/day, and adjust in increments of no more than 1 mg/week.

Maintain the dose within the range of 1-4 mg once daily, depending on clinical response and tolerability. In clinical trials, patients were randomized to doses of 1 mg, 2 mg, 3 mg or 4 mg and received INTUNIV™ once daily in the morning [see *Clinical Studies (14.1)*].

Clinically relevant improvements were observed beginning at doses in the range 0.05-0.08 mg/kg once daily. Efficacy increased with increasing weight-adjusted dose (mg/kg). If well tolerated, doses up to 0.12 mg/kg once daily may provide additional benefit. Doses above 4mg/day have not been studied.

In clinical trials, there were dose-related and exposure-related risks for several clinically significant adverse reactions (hypotension, bradycardia, sedative events). Thus, consideration should be given to dosing INTUNIV™ on a mg/kg basis, in order to balance the exposure-related potential benefits and risks of treatment.

2.3 Maintenance Treatment

The effectiveness of INTUNIV™ for longer-term use (more than 9 weeks) has not been systematically evaluated in controlled trials. Therefore the physician electing to use INTUNIV™ for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

2.4 Discontinuation

In a pharmacodynamic study in healthy young adult volunteers receiving INTUNIV™ (4 mg once daily) or placebo, the effects of abrupt discontinuation were compared to tapering. There were greater mean increases in systolic and diastolic blood pressure and heart rate after abrupt discontinuation of INTUNIV™, but these changes generally reflected a return to original baseline and were not meaningfully different for the two discontinuation strategies. However, infrequent, transient elevations in blood pressure above original baseline (i.e., rebound) have been reported to occur upon abrupt discontinuation of guanfacine. To minimize these effects, the dose should generally be tapered in decrements of no more than 1 mg every 3 to 7 days.

2.5 Missed Doses

When reinitiating patients to the previous maintenance dose after two or more missed consecutive doses, physicians should consider titration based on patient tolerability.

3 DOSAGE FORMS AND STRENGTHS

1 mg, 2 mg, 3 mg and 4 mg extended-release tablets

	1 mg	**2 mg**	**3 mg**	**4 mg**
Color	White/off-white	White/off-white	Green	Green
Shape	Round	Caplet	Round	Caplet
Debossment (top/ bottom)	503 / 1mg	503 / 2mg	503 / 3mg	503 / 4mg

4 CONTRAINDICATIONS

Patients with a history of hypersensitivity to INTUNIV™, its inactive ingredients [see *Description (11)*], or other products containing guanfacine (e.g. TENEX®) should not take INTUNIV™.

5 WARNINGS AND PRECAUTIONS

5.1 Hypotension, Bradycardia, and Syncope

Treatment with INTUNIV™ can cause decreases in blood pressure and heart rate. In the pediatric, short-term (8-9 weeks), controlled trials, the maximum mean changes from baseline in systolic blood pressure, diastolic blood pressure, and pulse were -5 mm Hg, -3 mm Hg, and -6 bpm, respectively, for all dose groups combined (generally one week after reaching target doses of 1 mg/day, 2 mg/ day, 3 mg/day or 4 mg/day). These changes were dose dependent. Decreases in blood pressure and heart rate were usually modest and asymptomatic; however, hypotension and bradycardia can occur. Hypotension was reported as an adverse event for 6% of the INTUNIV™ group and 4% of the placebo group. Orthostatic hypotension was reported for 1% of the INTUNIV™ group and none in the placebo group. In long-term, open label studies, (mean exposure of approximately 10 months), maximum decreases in systolic and diastolic blood pressure occurred in the first month of therapy. Decreases were less pronounced over time. Syncope occurred in 1% of pediatric subjects in the clinical program. The majority of these cases occurred in the long-term, open-label studies.

Measure heart rate and blood pressure prior to initiation of therapy, following dose increases, and periodically while on therapy. Use INTUNIV™ with caution in patients with a history of hypotension, heart block, bradycardia, or cardiovascular disease, because it can decrease blood pressure and heart rate. Use caution in treating patients who have a history of syncope or may have a condition that predisposes them to syncope, such as hypotension, orthostatic hypotension, bradycardia, or dehydration. Use INTUNIV™ with caution in patients treated concomitantly with antihypertensives or other drugs that can reduce blood pressure or heart rate or increase the risk of syncope. Advise patients to avoid becoming dehydrated or overheated.

5.2 Sedation and Somnolence

Somnolence and sedation were commonly reported adverse reactions in clinical studies (38% for INTUNIV™ vs. 12% for placebo) in children and adolescents with ADHD, especially during initial use [see *Adverse Reactions (6.1)*]. Before using INTUNIV™ with other centrally active depressants (such as phenothiazines, barbiturates, or benzodiazepines), consider the potential for additive sedative effects. Caution patients against operating heavy equipment or driving until they know how they respond to treatment with INTUNIV™. Advise patients to avoid use with alcohol.

5.3 Other Guanfacine-Containing Products

Guanfacine, the active ingredient in INTUNIV™, is also approved as an antihypertensive. Do not use INTUNIV™ in patients concomitantly taking other guanfacine-containing products (e.g., Tenex).

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labelling:

- Hypotension, bradycardia, and syncope [see *Warnings and Precautions (5.1)*]
- Sedation and somnolence [see *Warnings and Precautions (5.2)*]

The most common adverse reactions with INTUNIV™ are: somnolence/sedation, abdominal pain, dizziness, hypotension/decreased blood pressure, dry mouth, and constipation.
Twelve percent (12%) of patients receiving INTUNIV™ discontinued from the clinical studies due to adverse events, compared to 4% in the placebo group. The most common adverse reactions leading to discontinuation of INTUNIV™-treated patients from the studies were somnolence/sedation (6%) and fatigue (2%). Less common adverse reactions leading to discontinuation (occurring in approximately 1% of patients) included: hypotension/decreased blood pressure, headache, and dizziness.

6.1 Clinical Trial Experience

Short Term Clinical Studies

Common Adverse Reactions - Two short-term, placebo-controlled, double-blind pivotal studies (Studies 1 and 2) were conducted in children and adolescents with ADHD, using fixed doses of INTUNIV™ (1, 2, 3, and 4 mg/day). The most commonly reported adverse reactions (occurring in ≥ 2% of patients) that were considered drug-related and reported in a greater percentage of patients taking INTUNIV™ compared to patients taking placebo are shown in Table 1. Adverse reactions that were dose related include: somnolence, sedation, abdominal pain, dizziness, hypotension/decreased blood pressure, dry mouth and constipation.

Table 1: Percentage of Patients Experiencing Common (≥2%) Adverse Reactions in Short-Term Studies 1 and 2

Adverse Reaction Term	Placebo (N=149)	All Doses of INTUNIV™ (N=513)
Somnolence[a]	12%	38%
Headache	19%	24%
Fatigue	3%	14%
Abdominal pain (upper)	7%	10%
Nausea	2%	6%
Lethargy	3%	6%
Dizziness	4%	6%
Irritability	4%	6%
Hypotension/Decreased blood pressure	4%	6%
Decreased appetite	3%	5%
Dry mouth	1%	4%
Constipation	1%	3%

a: The somnolence term includes somnolence, sedation, and hypersomnia.

Less Common Adverse Reactions - Less common adverse reactions (< 2%) reported in pivotal Studies 1 and 2 that occurred in more than one patient taking INTUNIV™ and were more common than in the placebo group are listed below.

Table 2: Less Common Adverse Reactions (< 2%) in Short-Term Studies 1 and 2

Body System	Adverse Reaction
Cardiac	Atrioventricular block, bradycardia, sinus arrhythmia
Gastrointestinal	Dyspepsia
General	Asthenia, chest pain
Investigations	Increased alanine aminotransferase, increased blood pressure, increased weight
Nervous system	Postural dizziness
Renal	Increased urinary frequency, enuresis
Respiratory	Asthma
Vascular	Orthostatic hypotension, pallor

In addition, the following less common (< 2%) psychiatric disorders occurred in more than one patient receiving INTUNIV™ and were more common than in the placebo group. The relationship to INTUNIV™ could not be determined because these events may also occur as symptoms in pediatric patients with ADHD: agitation, anxiety, depression, emotional lability, nightmares or interrupted sleep.

Long Term Clinical Studies

Common Adverse Reactions

Patients from the two short-term, placebo-controlled studies 1 and 2 were eligible to participate in one of two long-term, flexible-dose, open-label studies. The mean duration of exposure of the 446 patients who received open-label treatment was approximately 10 months. The distribution of patients among the doses prior to tapering off upon completion of the study was 37%, 33%, 27% and 3% on 4 mg, 3 mg, 2 mg and 1 mg, respectively.

The most common adverse reactions (≥5%) reported during open label treatment are shown in Table 3.

Table 3: Percentage of Patients Experiencing Common (≥5%) Adverse Reactions during Long-Term (Up to 10 months), Flexible-dose, Open-Label Follow-up from Studies 1 and 2

Adverse Reaction Term	All Doses of INTUNIV™ (N=446)
Somnolence[a]	45%
Headache	26%
Fatigue	15%
Abdominal pain (upper)	11%
Hypotension / Decreased Blood Pressure	10%
Vomiting	9%
Dizziness	7%
Nausea	7%
Weight increased	7%
Irritability	6%

a: The somnolence term includes somnolence, sedation, and hypersomnia.

Adverse Reactions Leading to Discontinuation - Eighteen percent (18%) of patients receiving INTUNIV™ discontinued from long-term studies due to adverse events. The most frequent adverse reactions leading to discontinuation (≥2%) were somnolence (3%), syncopal events (2%), increased weight (2%), depression (2%), and fatigue (2%). Other adverse reactions leading to discontinuation in the long-term studies (occurring in approximately 1% of patients) included: hypotension/decreased blood pressure, sedation, headache, and lethargy.

Serious Adverse Reactions - In long-term open label studies, serious adverse reactions occurring in more than one patient were syncope (2%) and convulsion (0.4%).

Less Common, Adverse Reactions - Adverse reactions that occurred in < 5% of patients but ≥ 2% in open-label, long-term studies that are considered possibly related to INTUNIV™ include: syncopal events, constipation, stomach discomfort, hypertension/increased blood pressure, decreased appetite, diarrhea, dry mouth, lethargy, and insomnia.

Effects on Height, Weight, and Body Mass Index (BMI)

Patients taking INTUNIV™ demonstrated similar growth compared to normative data. Patients taking INTUNIV™ had a mean increase in weight of 1 kg (2 lbs) compared to those receiving placebo over a comparative treatment period. Patients receiving INTUNIV™ for at least 12 months in open-label studies gained an average of 8 kg (17 lbs) in weight and 8 cm (3 in) in height. The height, weight, and BMI percentile remained stable in patients at 12 months in the long-term studies compared to when they began receiving INTUNIV™.

Laboratory Tests

In short and long-term studies, no clinically important effects were identified on any laboratory parameters.

Effects on Heart Rate and QT Interval

The effect of two dose levels of immediate-release guanfacine (4 mg and 8 mg) on the QT interval was evaluated in a double-blind, randomized, placebo- and active-controlled, cross-over study in healthy adults.

A dose-dependent decrease in heart rate was observed during the first 12 hours, at time of maximal concentrations. The mean change in heart rate was -13 bpm at 4 mg and -22 bpm at 8 mg.

An apparent increase in mean QTc was observed for both doses. However, guanfacine does not appear to interfere with cardiac repolarization of the form associated with pro-arrhythmic drugs. This finding has no known clinical relevance.

7 DRUG INTERACTIONS

7.1 CYP3A4/5 Inhibitors

Use caution when INTUNIV™ is administered to patients taking ketoconazole and other strong CYP3A4/5 inhibitors, since elevation of plasma guanfacine concentration increases the risk of adverse events such as hypotension, bradycardia, and sedation. There was a substantial increase in the rate and extent of guanfacine exposure when administered with ketoconazole; the guanfacine exposure increased 3-fold (AUC).

7.2 CYP3A4 Inducers
When patients are taking INTUNIV™ concomitantly with a CYP3A4 inducer, an increase in the dose of INTUNIV™ within the recommended dose range may be considered. There was a significant decrease in the rate and extent of guanfacine exposure when co-administered with rifampin, a CYP3A4 inducer. The exposure to guanfacine decreased by 70% (AUC).

7.3 Valproic Acid
Co-administration of guanfacine and valproic acid can result in increased concentrations of valproic acid. The mechanism of this interaction is unknown, although both guanfacine (via a Phase I metabolite, 3-hydroxy guanfacine) and valproic acid are metabolized by glucuronidation, possibly resulting in competitive inhibition. When INTUNIV™ is co-administered with valproic acid, monitor patients for potential additive CNS effects, and consider monitoring serum valproic acid concentrations. Adjustments in the dose of valproic acid may be indicated when co-administered with INTUNIV™.

7.4 Antihypertensive Drugs
Use caution when INTUNIV™ is administered concomitantly with antihypertensive drugs, due to the potential for additive pharmacodynamic effects. (e.g., hypotension, syncope) [see *Warnings and Precautions (5.1)*].

7.5 CNS Depressant Drugs
Caution should be exercised when INTUNIV™ is administered concomitantly with CNS depressant drugs (e.g. alcohol, sedative/ hypnotics, benzodiazepines, barbiturates, and antipsychotics) due to the potential for additive pharmacodynamic effects. (e.g., sedation, somnolence) [see *Warnings and Precautions (5.2)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Pregnancy Category B
Rat experiments have shown that guanfacine crosses the placenta. However, administration of guanfacine to rats and rabbits at 6 and 4 times, respectively, the maximum recommended human dose of 4 mg/day on a mg/m^2 basis resulted in no evidence of harm to the fetus. Higher doses (20 times the maximum recommended human dose in both rabbits and rats) were associated with reduced fetal survival and maternal toxicity. There are no adequate and well-controlled studies of guanfacine in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers
It is not known whether guanfacine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when INTUNIV™ is administered to a nursing woman. Experiments with rats have shown that guanfacine is excreted in the milk.

8.4 Pediatric Use
The safety and efficacy of INTUNIV™ in pediatric patients less than 6 years of age have not been established. For children and adolescents 6 years and older, efficacy beyond 9 weeks and safety beyond 2 years of treatment have not been established [see *Adverse Reactions (6)* and *Clinical Studies (14)*].

8.5 Geriatric Use
The safety and efficacy of INTUNIV™ in geriatric patients have not been established.

8.6 Use in Patients with Renal or Hepatic Impairment
Renal Impairment
The impact of renal impairment on the pharmacokinetics of guanfacine in children was not assessed. In adult patients with impaired renal function, the cumulative urinary excretion of guanfacine and the renal clearance diminished as renal function decreased. In patients on hemodialysis, the dialysis clearance was about 15% of the total clearance. The low dialysis clearance suggests that the hepatic elimination (metabolism) increases as renal function decreases. It may be necessary to adjust the dose in patients with significant impairment of renal function.
Hepatic Impairment
The impact of hepatic impairment on PK of guanfacine in children was not assessed. Guanfacine in adults is cleared both by the liver and the kidney, and approximately 50% of the clearance of guanfacine is hepatic. It may be necessary to adjust the dose in patients with significant impairment of hepatic function.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance
INTUNIV™ is not a controlled substance and has no known potential for abuse or dependence.

10 OVERDOSAGE

Symptoms

Two cases of accidental overdose of INTUNIV™ were reported in clinical trials in pediatric ADHD patients. These reports included adverse reactions of sedation and bradycardia in one patient and somnolence and dizziness in the other patient.

During post-marketing surveillance of guanfacine as an antihypertensive treatment for adults, drowsiness, lethargy, bradycardia and hypotension have been observed following overdose. Similar symptoms have been described in voluntary reports to the American Association of Poison Control Center's National Poison Data System. Miosis of the pupils may be noted on examination**.** No fatal overdoses of guanfacine have been reported in published literature.

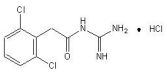
Treatment

Consult a Certified Poison Control Center for up to date guidance and advice. Gastric lavage may be indicated if performed soon after ingestion. Activated charcoal may be useful in limiting absorption. Guanfacine is not dialyzable in clinically significant amounts (2.4%).

Management of INTUNIV™ overdose should include monitoring for and the treatment of hypotension, bradycardia, lethargy and respiratory depression. Children and adolescents who develop lethargy should be observed for the development of more serious toxicity including coma, bradycardia and hypotension for up to 24 hours, due to the possibility of delayed onset hypotension.

11 DESCRIPTION

INTUNIV™ is a once-daily, extended-release formulation of guanfacine hydrochloride (HCl) in a matrix tablet formulation for oral administration only. The chemical designation is N-amidino-2-(2,6-dichlorophenyl) acetamide monohydrochloride. The molecular formula is $C_9H_9Cl_2N_3O \cdot HCl$ corresponding to a molecular weight of 282.55. The chemical structure is:



Guanfacine HCl is a white to off-white crystalline powder, sparingly soluble in water (approximately 1 mg/mL) and alcohol and slightly soluble in acetone. The only organic solvent in which it has relatively high solubility is methanol (>30 mg/mL). Each tablet contains guanfacine HCl equivalent to 1 mg, 2 mg, 3 mg, or 4 mg of guanfacine base. The tablets also contain hypromellose, methacrylic acid copolymer, lactose, povidone, crospovidone, microcrystalline cellulose, fumaric acid, and glyceryl behenate. In addition, the 3mg and 4mg tablets also contain green pigment blend PB-1763.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Guanfacine is a selective $alpha_{2A}$-adrenergic receptor agonist. Guanfacine is not a central nervous system (CNS) stimulant. The mechanism of action of guanfacine in ADHD is not known.

12.2 Pharmacodynamics

Guanfacine is a selective $alpha_{2A}$-adrenergic receptor agonist in that it has a 15-20 times higher affinity for this receptor subtype than for the $alpha_{2B}$ or $alpha_{2C}$ subtypes.

Guanfacine is a known antihypertensive agent. By stimulating $alpha_{2A}$-adrenergic receptors, guanfacine reduces sympathetic nerve impulses from the vasomotor center to the heart and blood vessels. This results in a decrease in peripheral vascular resistance and a reduction in heart rate.

12.3 Pharmacokinetics

Absorption and Distribution

Guanfacine is readily absorbed and approximately 70% bound to plasma proteins independent of drug concentration. After oral administration of INTUNIV™ the time to peak plasma concentration is approximately 5 hours in children and adolescents with ADHD.

Immediate-release guanfacine and INTUNIV™ have different pharmacokinetic characteristics; dose substitution on a milligram for milligram basis will result in differences in exposure.

A comparison across studies suggests that the C_{max} is 60% lower and $AUC_{0-\infty}$ 43% lower, respectively, for INTUNIV™ compared to immediate-release guanfacine. Therefore, the relative bioavailability of INTUNIV™ to immediate-release guanfacine is 58%.

The mean pharmacokinetic parameters in adults following the administration of INTUNIV™ 1 mg once daily and immediate-release guanfacine 1mg once daily are summarized in Table 4.

Table 4: Pharmacokinetic Parameters in Adults

Parameter	**INTUNIV™ 1 mg once daily (n=52)**	**Immediate-release guanfacine 1 mg once daily (n=12)**

C_{max} (ng/mL)	1.0 ± 0.3	2.5 ± 0.6
$AUC_{0-\infty}$ (ng.h/mL)	32 ± 9	56 ± 15
t_{max} (h)	6.0 (4.0 - 8.0)	3.0 (1.5-4.0)
$t_{1/2}$ (h)	18 ± 4	16 ± 3
Note: Values are mean +/- SD, except for t_{max} which is median (range)		

Exposure to guanfacine was higher in children (ages 6-12) compared to adolescents (ages 13-17) and adults. After oral administration of multiple doses of INTUNIV™ 4 mg, the C_{max} was 10 ng/mL compared to 7 ng/mL and the AUC was 162 ng h/mL compared to 116 ng h/mL in children (ages 6-12) and adolescents (ages 13-17), respectively. These differences are probably attributable to the lower body weight of children compared to adolescents and adults.

The pharmacokinetics were affected by intake of food when a single dose of INTUNIV™ 4 mg was administered with a high-fat breakfast. The mean exposure increased (C_{max} ~75% and AUC ~40%) compared to dosing in a fasted state.

Dose Proportionality

Following administration of INTUNIV™ in single doses of 1 mg, 2 mg, 3 mg, and 4 mg to adults, C_{max} and $AUC_{0-\infty}$ of guanfacine were proportional to dose.

Metabolism and Elimination

In vitro studies with human liver microsomes and recombinant CYP's demonstrated that guanfacine was primarily metabolized by CYP3A4. In pooled human hepatic microsomes, guanfacine did not inhibit the activities of the major cytochrome P450 isoenzymes (CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4/5). Guanfacine is a substrate of CYP3A4/5 and exposure is affected by CYP3A4/5 inducers/inhibitors.

Renal and Hepatic Impairment

The impact of renal impairment on PK of guanfacine in children was not assessed [*see Use in Specific Populations (8.6)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenic effect of guanfacine was observed in studies of 78 weeks in mice or 102 weeks in rats at doses up to 6-7 times the maximum recommended human dose of 4 mg/day on a mg/ m^2 basis.

Guanfacine was not genotoxic in a variety of test models, including the Ames test and an *in vitro* chromosomal aberration test; however, a marginal increase in numerical aberrations (polyploidy) was observed in the latter study.

No adverse effects were observed in fertility studies in male and female rats at doses up to 30 times the maximum recommended human dose on a mg/ m^2 basis.

14 CLINICAL STUDIES

14.1 Safety and Efficacy Studies

The efficacy of INTUNIV™ in the treatment of ADHD was established in 2 placebo-controlled trials in children and adolescents ages 6-17. Study 1 evaluated 2 mg, 3 mg and 4 mg of INTUNIV™ dosed once daily in an 8-week, double-blind, placebo-controlled, parallel-group, fixed dose design (n=345). Study 2 evaluated 1 mg, 2 mg, 3 mg and 4 mg of INTUNIV™ dosed once daily in a 9-week, double-blind, placebo-controlled, parallel-group, fixed-dose design (n=324). In Studies 1 and 2, patients were randomized to a fixed dose of INTUNIV™. Doses were titrated in increments of up to 1 mg/week. The lowest dose of 1 mg used in Study 2 was assigned only to patients less than 50 kg (110 lbs). Patients who weighed less than 25 kg (55 lbs) were not included in either study. Signs and symptoms of ADHD were evaluated on a once weekly basis using the clinician administered and scored ADHD Rating Scale-IV (ADHD-RS), which includes both hyperactive/impulsive and inattentive subscales. In both studies, the primary outcome was the change from baseline to endpoint in mean ADHD-RS scores.

The mean reductions in ADHD-RS scores at endpoint were statistically significantly greater for INTUNIV™ compared to placebo for Studies 1 and 2. Placebo-adjusted changes from baseline were statistically significant for each of the 2 mg, 3 mg, and 4 mg INTUNIV™ randomized treatment groups in both studies, as well as the 1 mg INTUNIV™ treatment group (for patients 55-110 lbs) that was included only in Study 2.

Dose-responsive efficacy was evident, particularly when data were examined on a weight-adjusted (mg/kg) basis. When evaluated over the dose range of 0.01-0.17 mg/kg/day, clinically relevant improvements were observed beginning at doses in the range 0.05-0.08 mg/kg/day. Doses up to 0.12 mg/kg/day were shown to provide additional benefit.

Controlled, long-term efficacy studies (>9 weeks) have not been conducted.

Subgroup analyses were performed to identify any differences in response based on gender or age (6-12 vs. 13-17). Analyses of the primary outcome did not suggest any differential responsiveness on the basis of gender. Analyses by age subgroup revealed a statistically significant treatment effect only in the 6-12 age subgroup. Due to the relatively small proportion of adolescent patients (ages 13-17) enrolled into these studies (approximately 25%), these data may not be sufficient to demonstrate efficacy in the

adolescent subgroup. In these studies, patients were randomized to a fixed dose of INTUNIV™ rather than optimized by body weight. Therefore, it is likely that some adolescent patients were randomized to a dose that resulted in relatively low plasma guanfacine concentrations compared to the younger sub-group. Over half (55%) of the adolescent patients received doses of 0.01-0.04mg/kg. In studies in which systematic pharmacokinetic data were obtained, there was a strong inverse correlation between body weight and plasma guanfacine concentrations.

16 HOW SUPPLIED/STORAGE AND HANDLING

INTUNIV™ is supplied in 1 mg, 2 mg, 3 mg, and 4 mg strength extended-release tablets in 100 count bottles.

	1 mg	2 mg	3 mg	4 mg
Color	White/off-white	White/off-white	Green	Green
Shape	Round	Caplet	Round	Caplet
Debossment (top/ bottom)	503 / 1mg	503 / 2mg	503 / 3mg	503 / 4mg
NDC number	54092-513-02	54092-515-02	54092-517-02	54092-519-02

Storage - Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). See USP Controlled Room Temperature.

17 PATIENT COUNSELING INFORMATION

[See FDA-Approved Patient Labeling.]

17.1 Dosing and Administration

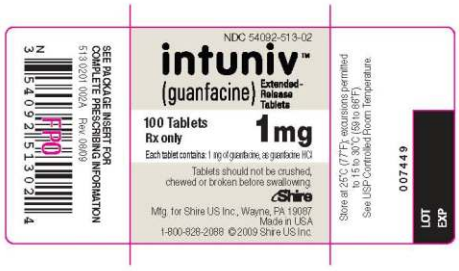
Instruct patients to swallow INTUNIV™ whole with water, milk or other liquid. **Tablets should not be crushed, chewed or broken prior to administration because this may increase the rate of release of the active drug.** Patients should not take INTUNIV™ together with a high-fat meal, since this can raise blood levels of INTUNIV™. Instruct the parent or caregiver to supervise the child or adolescent taking INTUNIV™ and to keep the bottle of tablets out of reach of children.
Instruct patients on how to properly taper the medication, if the physician decides to discontinue treatment.

17.2 Adverse Reactions

Advise patients that sedation can occur, particularly early in treatment or with dose increases. Caution against operating heavy equipment or driving until they know how they respond to treatment with INTUNIV™. Headache and abdominal pain can also occur. If any of these symptoms persist, or other symptoms occur, the patient should be advised to discuss the symptoms with the physician. Advise patients to avoid becoming dehydrated or overheated, and to avoid use with alcohol.

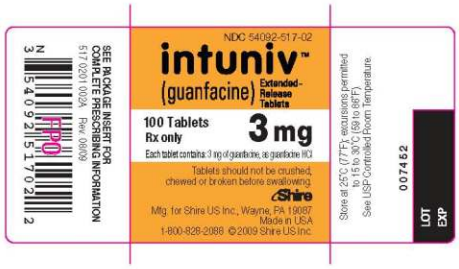
CONTAINER LABELS

DSM 100 Count 1 mg



DSM 100 Count 2 mg

DSM 100 Count 3 mg



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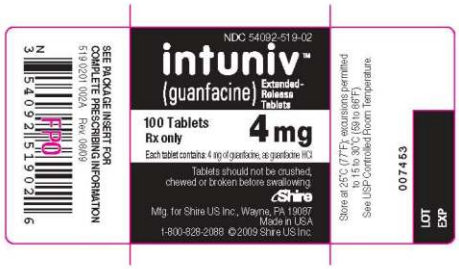


DSM Physician Sample 7 Count 1 mg

FRONT

INSIDE

BASE

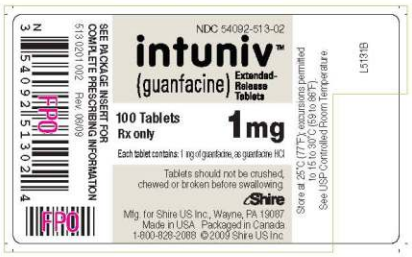
DSM Physician Sample 7 Count 2 mg

FRONT

INSIDE

BASE

WellSpring 100 Count 1 mg



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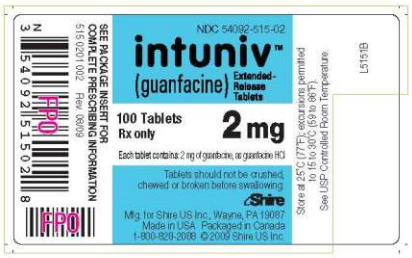

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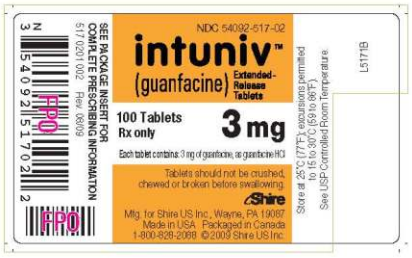

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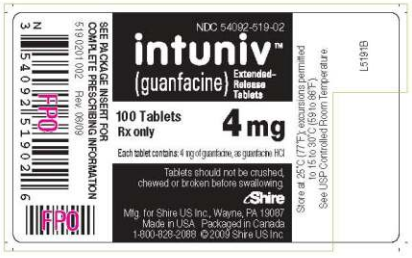
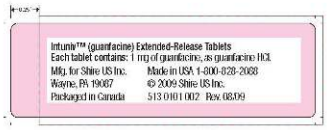


WellSpring Physician Sample 7 Count 1 mg

TOP

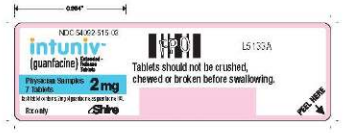
INSIDE

BASE



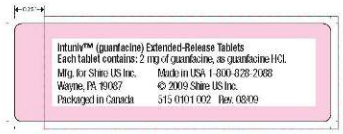
WellSpring Physician Sample 7 Count 2 mg

TOP



INSIDE

BASE



PATIENT INFORMATION
INTUNIV™ (in-TOO-niv)
(guanfacine)
Extended-Release Tablets

Read the Patient Information that comes with INTUNIV™ before you start taking it and each time you get a refill. There may be new information. **This leaflet does not take the place of talking with your doctor about your medical condition or your treatment.**

What is INTUNIV™?

INTUNIV™ is a prescription medicine used to treat the symptoms of attention deficit/hyperactivity disorder (ADHD).
INTUNIV™ is not a central nervous system (CNS) stimulant.
INTUNIV™ should be used as a part of a total treatment program for ADHD that may include counselling or other therapies.
It is not known if INTUNIV™ is effective:
for use longer than 9 weeks
It is not known if INTUNIV™ is safe or effective:
in children younger than 6 years old
in adults

What should I tell my doctor before taking INTUNIV™?

Before you take INTUNIV™, tell your doctor if you:

- have heart problems or a low heart rate
- have fainted
- have low blood pressure
- have liver or kidney problems
- have any other medical conditions

- are pregnant or plan to become pregnant. It is not known if INTUNIV™ will harm your unborn baby. Talk to your doctor if you are pregnant or plan to become pregnant.

- are breast-feeding or plan to breast-feed. It is not known if INTUNIV™ passes into your breast milk. You and your doctor should decide if you will take INTUNIV™ or breastfeed.

Tell your doctor about all of the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.
INTUNIV™ may affect the way other medicines work, and other medicines may affect how INTUNIV™ works.
Especially tell your doctor if you take:
- ketoconazole

- medicines that can affect enzyme metabolism

- valproic acid

- high blood pressure medicine

- sedatives

- benzodiazepines

- barbiturates

- antipsychotics

Ask your doctor or pharmacist for a list of these medicines, if you are not sure.
Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.
How should I take INTUNIV™?
- Take INTUNIV™ exactly as your doctor tells you.

- Your doctor may change your dose. Do not change your dose of INTUNIV™ without talking to your doctor.

- Do not stop taking INTUNIV™ without talking to your doctor.

- INTUNIV™ should be taken 1 time a day.

- INTUNIV™ should be swallowed whole with a small amount of water, milk, or other liquid.

- Do not crush, chew, or break INTUNIV™. Tell your doctor if you can not swallow INTUNIV™ whole.

- Do not take INTUNIV™ with a high-fat meal.

- Your doctor will check your blood pressure and heart rate while you take INTUNIV™.

- If you take too much INTUNIV™, call your local Poison Control Center or go to the nearest emergency room right away.

What should I avoid while taking INTUNIV™?
- Do not drive, operate heavy machinery, or do other dangerous activities until you know how INTUNIV™ affects you. INTUNIV™ can slow your thinking and motor skills.

- Do not drink alcohol or take other medicines that make you sleepy or dizzy while taking INTUNIV™ until you talk with your doctor. INTUNIV™ taken with alcohol or medicines that cause sleepiness or dizziness may make your sleepiness or dizziness worse.

What are the possible side effects of INTUNIV™?
INTUNIV™ may cause serious side effects including:
- low blood pressure

- low heart rate

- fainting

- sleepiness

- tiredness
- drowsiness

Get medical help right away, if you have any of the symptoms listed above.

The most common side effects of INTUNIV™ include:

- sleepiness
- drowsiness
- low blood pressure
- headache
- nausea
- stomach pain
- dry mouth
- dizziness
- irritability
- constipation
- not hungry (decreased appetite)

Tell the doctor if you have any side effect that bothers you or that does not go away.
These are not all the possible side effects of INTUNIV™. For more information, ask your doctor or pharmacist.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store INTUNIV™?

- Store INTUNIV™ between 59^0F to 86^0F (15^oC to 30^oC)

Keep INTUNIV™ and all medicines out of the reach of children.

General Information about INTUNIV™

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. Do not use INTUNIV™ for a condition for which it was not prescribed. Do not give INTUNIV™ to other people, even if they have the same symptoms that you have. It may harm them.
This leaflet summarizes the most important information about INTUNIV™. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about INTUNIV™ that is written for health professionals.
For more information, go to **www.INTUNIV.com or call 1-800-828-2088.**

What are the ingredients in INTUNIV™?

Active ingredient: guanfacine hydrochloride
Inactive ingredients: hypromellose, methacrylic acid copolymer, lactose, povidone, crospovidone, microcrystalline cellulose, fumaric acid, and glycerol behenate. In addition, the 3mg and 4mg tablets also contain green pigment blend PB-1763.
Manufactured for Shire US Inc., Wayne, PA 19087.

Version: August 2009